IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Commissioner of Patents & Trademarks
Washington, D.C. 20231
Attn: Box Patent Application
Sir: This is a request for filing a

Docket No. **SCH-1615 D1**
Prior Application: 09/208,587
Examiner: G. Kun
Art Unit: 1623

☐ Continuation
☒ Divisional
application under 37 C.F.R. 1.53(b) of pending prior application Serial No. 09/208,587 filed on December 10, 1998 of Ulf TILSTAM et al., for "PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE LITHIUM, SODIUM, POTASSIUM, CALCIUM AND MAGNESIUM SALTS AN PURIFICATION PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE AND FLUDARABINE-PHOSPHATE WITH A PURITY OF AT LEAST 99.5%".

1. ☒ Enclosed are 11 pages of the specification including claims and zero (0) sheets of drawings.

2. ☒ Enclosed is a copy of the oath or declaration as originally filed in Serial No. 09/208,587 on December 10, 1998 in accordance with 37 C.F.R. §1.63(d).

3. ☒ The filing fee is calculated below:

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
TOTAL CLAIMS	6 - 20	0	$18	0
INDEPENDENT CLAIMS	1 - 3	0	$78	0
☐ MULTIPLE DEPENDENT CLAIM PRESENTED				
☐ Small Entity Status Claimed under 37 CFR 1.9 and 1.27			BASIC FEE	$760.00
Statement(s): ☐ Attached ☐ Filed in Parent			TOTAL FILING FEE	$760.00

4. ☒ The amount of $ 760.00 is included in the attached check.
   ☒ If a check is not attached, authorization is given to charge the amount indicated in the above sentence to Deposit Account No. 13-3402; two copies of this page being attached for this purpose.

5. ☒ An IDS and Preliminary Amendment are attached.

6. ☒ The Commissioner is hereby authorized to charge any deficiencies or credit any overpayment in payment of the following fees associated with this communication or otherwise due during the pendency of this application to Deposit Account No. 13-3402.
   ☒ Any filing fees under 37 CFR §1.16 for the presentation of extra claims.
   ☒ Any patent application processing fees under 37 CFR §1.17.

7. ☒ Cancel in this application original claims 1-4 of the prior application before calculating the filing fee.

8. ☒ Amend the specification by inserting before the first line the sentence:
   -- This is a division of application Serial No. 09/208,587 filed December 10, 1998 --.

9. ☒ Priority of application Serial No. 197 56 289.2 filed on December 11, 1997 in Germany and Serial No. 60/069,778 filed on December 16, 1997 in The United States is claimed under 35 U.S.C. §119.

10. ☒ The prior application is assigned of record to SCHERING AKTIENGESELLSCHAFT.

11. ☒ The power of attorney in the prior application is to I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E. J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-Cox (33,302); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); and Luan C. Do (38,434).
   ☒ a. The power appears in the original papers in the prior application.
   ☒ b. Address all future communications to MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

12. ☒ Incorporation By Reference.
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 2, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

Date: December 23, 1999

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Ulf TILSTAM et al.	:	Group Art Unit:
Serial No.: *not available*	:	Examiner:
Filed: December 23, 1999	:	

For: PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE LITHIUM, SODIUM, POTASSIUM, CALCIUM AND MAGNESIUM SALTS AN PURIFICATION PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE AND FLUDARABINE-PHOSPHATE WITH A PURITY OF AT LEAST 99.5%

PRELIMINARY AMDENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Prior to the examination of the above-identified application, please amend the application as follows:

IN THE CLAIMS:

Please cancel claims 1-4.

In Claim 6, line 1, after "Fludarabine-phosphate" insert --of claim 5--.

In Claim 7, line 1, after "Fludarabine-phosphate" insert --of claim 5--.

In Claim 8, line 1, after "Fludarabine-phosphate" insert --of claim 5--.

In Claim 9, line 1, after "Fludarabine-phosphate" insert --of claim 5--.

In Claim 10, line 1, after "Fludarabine-phosphate" insert --of claim 5--.

REMARKS

The purpose of this Preliminary Amendment is to reduce the number of independent claims.

Respectfully submitted,

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Filed: December 23, 1999

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Process for the Production of Fludarabine-Phosphate Lithium, Sodium, Potassium, Calcium and Magnesium Salts and Purification Process for the Production of Fludarabine-Phosphate and Fludarabine-Phosphate with a Purity of at Least 99.5%

The invention relates to a process for the production of fludarabine-phosphate lithium, sodium, potassium, calcium and magnesium salts that can be used as intermediate products for the purification of FLUDARABINE-PHOSPHATE, and fludarabine-phosphate with a purity of at least 99.5%.

Fludarabine-phosphate is the "International Nonproprietary Name" (INN) of 9-ß-D-arabinofuranosyl-2-fluoroadenine-5'-O-dihydrogenphosphate. The first synthesis of the precursor of fludarabine-phosphate, 9-ß-D-arabinofuranosyl-2-fluoroadenine, is described in US-PS 4,188,378. This substance has strongly cytotoxic properties, and various derivatives of it were produced with the purpose of reducing side-effects. The 5'-phosphate (prodrug), thus the fludarabine-phosphate and its production, is described within US-PS 4,357,324. In further publications, for example US-PS 4,210,745, WO 91/08215 and WO 94/12514, alternative production processes are disclosed.

The production method that is used at this time starts from 9-ß-D-arabinofuranosyl-2-fluoroadenine that is reacted with trimethylphosphate and phosphoroxychloride (phosphorylation). These educts are brought to reaction and then crystallized from water. The temperature of approximately 75°C that is to be used in the recrystallization destroys a portion of the substance,

since fludarabine-phosphate is thermally unstable in water at this temperature. It is further disadvantageous that this recrystallization that is known from the prior art results only in weak improvement of purity, and even for technical production, the process can be implemented only in batch sizes of approximately below 1 kg. The salts of fludarabine-phosphate that are described within DE 41 41 454 A1 cannot be produced according to the teaching of this publication. If the described reaction conditions were used, mainly cleavage of phosphoric acid in the molecule would result.

In US 5,296,589, the water solubility of the sodium salt of fludarabine-phosphate (2-fluoro-ara-adenosine 5′-phosphate) is described in column 10, lines 37-40. It is further described in column 9, lines 61-69 that the salt cannot be purified by recrystallization from water, since these conditions would result in destroying the compound (see also DE 195 43 052 A1, WO 92/0312 A1 and US 5,506,352).

The object of this invention is to provide a purification process that results in considerably improved quality (purity) of fludarabine-phosphate and that in an industrial-scale process can easily be applied even to quantities of more than one kilogram.

This object is achieved according to the teaching of the claims.

The invention relates to a process for the production of fludarabine-phosphate lithium, sodium, potassium, calcium and magnesium salts, whereby fludarabine-phosphate is suspended in water, an alkali or alkaline-earth basic solution is added to

this solution while being stirred and at temperatures of below 30°C, and this solution is slowly poured into acetone that is 45-55°C, cooled, and the deposited precipitate is optionally filtered and optionally dried, and further to a process for the production of fludarabine-phosphate, whereby the lithium, sodium, potassium, calcium and magnesium salts are produced according to claim 1 and then are released with mineral acid.

Used as suitable bases are hydroxides and carbonates of alkalis or alkaline-earths, which are readily soluble in water; for example, lithium, sodium, potassium or calcium hydroxide; sodium or potassium carbonate.

As has been found, surprisingly enough, alkali and alkaline-earth salts of fludarabine-phosphate can be produced as stable, crystalline and readily characterizable substances that can be purified by crystallization. It has been shown that these alkali and alkaline-earth salts of fludarabine-phosphate can be isolated with ease; the latter withstand even prolonged storage without showing instability. Especially suitable are lithium, sodium, potassium, calcium and magnesium salts.

Here, it has proven to be advantageous that this crystallization takes place especially readily from water/acetone. Thus, fludarabine-phosphate is dissolved by adding sodium carbonate solution or the analogous basic solutions of the other elements and is poured into this aqueous solution in acetone. For example, 6.1 kg of fludarabine-phosphate is suspended in 35 l of water; 1.79 kg of sodium carbonate, dissolved in 7.9 l of water, is added, and this solution is

poured into 150 l of acetone at 45-55°C, preferably at 50°C. The temperature must never exceed 60°C, since otherwise the substitution of fluorine by hydroxyl is carried out as a secondary reaction, which is undesirable. When the mixture is cooled, the NON-phosphated derivatives remain in solution, and the desired product crystallizes.

When dissolved in water, these fludarabine-phosphate salts of the alkalis and alkaline-earths produce solutions that are not strongly acidic but rather almost neutral. The recycling of these salts in free fludarabine-phosphate can easily be carried out by mixing with strong mineral acid. As mineral acids, for example, hydrochloric acid, sulfuric acid, nitric acid or phosphoric acid are used. When the free bases are released, the MULTIPLY phosphated by-products remain in solution.

The claimed salts of fludarabine-phosphate can easily be stored as precursors of fludarabine-phosphate for a prolonged time, and the active ingredients are released if necessary.

The invention also relates to fludarabine-phosphate with a purity of at least 99.5%. According to the prior art, the active ingredient previously could be obtained only at a purity of about 98.0-98.5%. It is impossible, by the conventional crystallization process, for example from water, to exceed a degree of purity of 98.5%, even though the same batch is crystallized several times. This conventional purification method is problematical in nature if the period for heating and filtration of the, for example, aqueous solution requires too much time; these are periods of 25 minutes and more. In this

case, it results in the formation of various contaminants, rubberlike materials, which can no longer be removed by crystallization methods.

Fludarabine-phosphate purities of, for example, 99.5; 99.55; 99.6; 99.65; 99.7; 99.75; 99.8; 99.9 or 99.95% can be obtained by the process according to the invention, even if fludarabine-phosphate is purified only one time according to the process of the invention. It is also possible, however, to use the process for a fludarabine-phosphate batch two and more times.

The following examples are intended to explain the invention in more detail:

EXAMPLE 1

FLUDARABINE-PHOSPHATE-DISODIUM SALT

5.0 g of fludarabine-phosphate at a purity of 98.5% is suspended in 30 ml of water and stirred for about 3-5 minutes. 6.5 ml of a soda solution (18.5% by weight) is added to this suspension while being stirred and at temperatures of below 30°C. After the addition has been completed, the mixture is stirred for 15 minutes and then undissolved material is filtered out. The clear solution that is thus obtained is slowly poured into acetone (at 50°C). It is stirred for 2 more hours and cooled. The deposited precipitate is filtered, washed with acetone and dried; 5.0 g of fludarabine-phosphate disodium salt, 98% of theory, is obtained.

Melting point 235°C; purity: 98.5%

Analysis: Cld: for $C_{10}H_{11}FNa_2N_5O_7P \times 2H_2O$ (445.20)

C, 26.98; H, 3.39; F, 4.27; N, 15.73; P, 6.96; Na 10.33

Fnd: C 27.15; H 3.93; N 15.72; Na 9.65; P 6.15

IR (KBr): 3420, 3340, 3200, 2910, 1650, 1610, 1390, 1210, 1100 and 980 cm^{-1}.

NMR (D_2O): 4.05-4.22 m (3H; H-4′; both H-5′); 4.45-4.60 m (2H; H-2′ and H-3′); 6.2 d (1H; H-1′); 8.45 s (1H; H-8).

EXAMPLE 2

RELEASE OF FLUDARABINE-PHOSPHATE FROM THE DISODIUM SALT

5.0 g of fludarabine-phosphate disodium salt according to Example 1 is dissolved in 35 ml of water within 3-5 minutes. The solution is filtered, mixed slowly with 5 ml of hydrochloric acid (37%) and stirred for 1-2 hours. The deposited precipitate is suctioned off and washed with ice water and ethanol, and 4.0 g of fludarabine-phosphate, 90% of theory, is produced.

Melting point 202-203°C; purity: 99.6%.

Analysis, Cld: $C_{10}H_{13}FN_5O_7P$ (365.21)

C, 32.89; H, 3.59; N, 19.17; F, 5.20: P 8.48

Fnd: C, 32.81; H, 3.65; N, 19.03; P, 8.41

IR (KBr): 3443, 3326, 3123, 2925, 2950-2100, 1663, 1591, 1211, 1126 and 1050 cm^{-1}.

NMR (DMSO): 3.94-3.99 m (1H; H-4′); 4.06-4.14 m (3H; H-3′; both H-5′); 4.14-4.18 m (1H; H-2′); 5.4-6.1 broad (OH protons); 6.17 d (1H; H-1′); 7.6-8.0 broad (NH protons); 8.14 s (1H; H-1′) 9-11 broad (P-OH).

EXAMPLE 3

FLUDARABINE-PHOSPHATE DILITHIUM SALT

10.0 g of fludarabine-phosphate at a purity of 97.4% is suspended in 70 ml of water within about 5 minutes and mixed with an aqueous lithium-hydroxide solution (10%). This solution is stirred for one hour at room temperature and then filtered. The clear solution that is thus obtained is poured into 250 ml of acetone (at 50°C) and stirred for 1 more hour. The deposited precipitate is filtered, washed with acetone and after drying, 4.3 g of fludarabine-phosphate-dilithium salt is produced. (90% of theory).

Melting point 240-260°C; purity: 98.5%.

Analysis: Cld: for $C_{10}H_{11}FLi_2N_5O_7P \times 3H_2O$ (431.12)

C, 27.86; H, 3.98; F, 4.41; N, 16.25; P, 7.18; Li, 3.22

Fnd: C 27.15; H 3.86; N 15.76; Li, 3.05; P 6.72

NMR (D_2O): 4.05-4.22 m (H-4′; H-5′); 4.45-4.55 m (H-2′ and H-3′); 6.25 d (H-1′); 8.50 s (H-8)

The release according to Example 2 results in a fludarabine-phosphate purity of 99.85%.

EXAMPLE 4

FLUDARABINE-PHOSPHATE-DIPOTASSIUM SALT

5.0 g of fludarabine-phosphate at a purity of 96.1% is dissolved in 30 ml of water, and 6.5 ml of a potassium carbonate solution (18.5% by weight) is added to this solution below 30°C. It is stirred for 15 more minutes, then solid material is filtered out. The clear solution that is thus obtained is poured

into acetone at 50°C, cooled to room temperature and stirred for 2 more hours. The deposited precipitate is filtered and washed twice with acetone. 4.5 g of fludarabine-phosphate dipotassium salt is obtained.

Melting point 220-230°C; purity: 98.55%.

IR (KBr): 3420, 3340, 3200, 2910, 1650, 1610, 1390, 1210, 1100 and 980 cm^{-1}.

NMR (D_2O): 4.0-4.2 m (H-4′; H-5′); 4.4-4.60 m (H-2′ and H-3′); 6.25 d (H-1′); 8.5 s (H-8).

The release according to Example 2 results in a fludarabine-phosphate purity of 99.80%.

EXAMPLE 5

FLUDARABINE-MAGNESIUM SALT:

10.0 g of fludarabine phosphate at a purity of 97.5% is suspended in 100 ml of water within about 5 minutes, and magnesium oxide is added to this solution. The mixture is stirred for one more hour at room temperature and then filtered. The clear solution is poured into 200 ml of acetone, stirred for 1 more hour, and the crystallizate is separated by filtration. 10.0 g (95% of theory) of the fludarabine-phosphate magnesium salt is obtained.

Melting point: 260°C; purity: 98.45%.

Analysis: Cld., for $C_{10}H_{11}FMgN_5O_7P \times 2H_2O$ (423, 525)

C, 28.36; H, 3.57; F, 4.49; Mg, 5.74; N, 16.54; P, 7.31

Fnd: C, 27.99; H, 3.92; Mg, 5.54; N, 16.38;

IR (KBr): 3420, 3340, 3200, 2910, 1650, 1610, 1390, 1210, 1100 and 980 cm^{-1}.

NMR (D_2O): 4.0-4.2 m (H-4′; H-5′); 4.5-4.60 m (H-2′ and H-3′); 6.2 d (H-1′); 8.4 s (H-8).

The release according to Example 2 results in a fludarabine-phosphate purity of 99.55%.

Claims

1. Process for the production of fludarabine-phosphate lithium, sodium, potassium, calcium and magnesium salts, whereby fludarabine-phosphate is dissolved in water, an alkali or alkaline-earth basic solution is added to this solution while being stirred and at temperatures of below 30°C, and this solution is slowly poured into acetone that is 45-55°C, cooled, and the deposited precipitate is optionally filtered and optionally dried.

2. Process for the production of fludarabine-phosphate, whereby the lithium, sodium, potassium, calcium and magnesium salts are produced according to claim 1 and then are released with mineral acid.

3. Process for the production of fludarabine-phosphate, whereby the lithium, sodium, potassium, calcium and magnesium salts are produced in a form that is more stable in storage according to claim 1 and then are released with mineral acid.

4. Process for the purification of fludarabine-phosphate, whereby crude fludarabine-phosphate is dissolved in water, an alkali or alkaline-earth basic solution is added to this solution while being stirred and at temperatures of below 30°C, and this solution is slowly poured into acetone that is 45-55°C, cooled, and the deposited precipitate is filtered and optionally dried and is obtained in a form that is stable in storage as a lithium, sodium, potassium, calcium or magnesium salt, and then this form that is stable in storage is dissolved in water and acidified

with mineral acid, and the deposited precipitate is filtered and dried.

5. Fludarabine-phosphate with a purity of at least 99.5%.

6. Fludarabine-phosphate with a purity of greater than 99.55%.

7. Fludarabine-phosphate with a purity of greater than 99.6%.

8. Fludarabine-phosphate with a purity of greater than 99.7%.

9. Fludarabine-phosphate with a purity of greater than 99.8%.

10. Fludarabine-phosphate with a purity of greater than 99.85%.

COMBINED DECLARATION FOR ATENT APPLICATION AND POWER OF TORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER SCH-1615

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought of the invention entitled:

PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE LITHIUM, SODIUM, POTASSIUM, CALCIUM AND MAGENSIUM SALTS AND PURIFICATION PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE AND FLUDARABINE-PHOSPHATE WITH A PURITY OF AT LEAST 99,5%

the specification of which (check only one item below):

☒ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

☐ was filed as PCT international application

Number _____

on _____,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
GERMAN	197 56 289.2	11DEC97	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH-1615

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
60/069,778	16DEC97		XX	

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (*if any*)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-Cox (33,302); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); Luan C. Do (38,434) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send Correspondence to: MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
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205	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:
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206	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
	POST OFFICE ADDRESS	STREET:	CITY:	STATE & ZIP CODE/COUNTRY:

Combined Declaration for Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH-1615

207	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
210	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
211	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
212	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	DATE 23.11.98	SIGNATURE OF INVENTOR 207	DATE
SIGNATURE OF INVENTOR 202	DATE 19.11.98	SIGNATURE OF INVENTOR 208	DATE
SIGNATURE OF INVENTOR 203	DATE 19.11.98	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE